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Hypertrophic Osteoarthropathy and Intrathoracic Hodgkin Disease of Childhood

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Background. Hypertrophic osteoarthropathy (HOA), well known in adults, is rarely encountered in children. The clinical features include clubbing of the fingers and toes, arthritis, and painful periosteal new bone formation of the tubular bones. The association of malignant disorders with HOA is more common in adults than in children.

Case. In this paper, a 12-year-old boy with intrathoracic Hodgkin disease and HOA is presented and four other children with HOA and Hodgkin disease in the literature reviewed.

Discussion. The presence of HOA has been thought to be a bad prognostic sign, but complete remission of Hodgkin disease and regression of clinical signs and symptoms of HOA were attained in our patient after chemotherapy and radiotherapy, and continue during 9 months post-therapy follow-up.

Conclusions. HOA accompanying a malignant tumor in children is very rare. Only 5 cases have been associated with Hodgkin disease, including the present boy. It is important that patients with symptoms of HOA and an intrathoracic mass be examined carefully to rule out a malignancy. Med. Pediatr. Oncol. 29:578–581, 1997.

Key words: Hodgkin disease; hypertrophic osteoarthropathy

INTRODUCTION

Hypertrophic osteoarthropathy (HOA) is a syndrome characterized by clubbing of the fingers and toes, periosteal new bone formation of the long bones and polyarthritis [1,2]. The pathogenesis of HOA is unknown, although estrogens, circulatory factors, neurogenic factors, and growth hormone have been postulated to play a role [1]. While intrathoracic neoplasms are one of the major causes of HOA in adults, they are rarely associated with HOA in childhood [1–5]. To date, 27 cases of HOA in association with childhood neoplasias have been reported in the English literature [3,6–11]. Four of these cases were associated with intrathoracic Hodgkin disease [7–10].

In this report, a 12-year-old boy with Hodgkin disease and HOA is presented and the literature reviewed.

CASE REPORT

A 12-year-old white male was admitted to the hospital in July 1995, with 5-months history of clubbing of the fingers and toes bilaterally, pain, and swelling of the knees, elbows, wrists, and ankles, tenderness of the fingers, toes, and lower legs and 3-months history of cough, sweating at night, and weight loss. Past history and family history were unremarkable.

On physical examination he was well developed. His respiration and pulse rate were 24/min and 110/min, respectively. There was clubbing of the fingers and toes and marked swelling of the knees, elbows, wrists, and ankles. There was a 1 × 1 cm axillary lymphadenopathy. The spleen was palpable 2 cm from the left costal margin at the midclavicular line and the liver was palpable 2 cm from the right costal margin at the midclavicular line.

Laboratory studies were non-contributory, but chest X-ray films showed a mediastinal widening, and computerized axial tomography of the chest revealed lymphadenomegaly in the right paratracheal, pre- and subcarinal, posterior mediastinal and left hilar areas compressing the left pulmonary artery and bronchus (Fig. 1). Bone survey revealed diffuse periosteal reactions in the shaft and distal parts of the long bones (Fig. 2).

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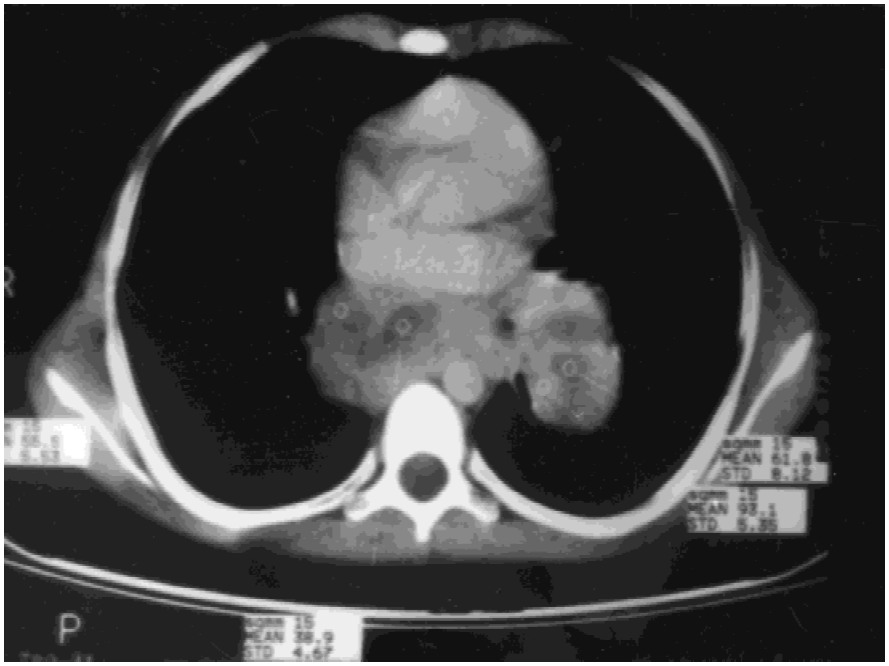

Fig. 1. A CT scan showing lymphadenopathy in the right paratracheal, pre- and sub-carinal, posterior mediastinal and left hilar areas, compressing the left pulmonary artery and bronchus.

The patient underwent a thoracotomy which revealed extensive mediastinal involvement with mixed cellular type Hodgkin disease. Subsequent staging laparotomy and splenectomy were performed. The patient was pathologically staged as III_{SB} and treated with six courses of MOPP/ABV hybrid chemotherapy regimen (nitrogen mustard 6 mg/m^2 i.v. 1st day; vincristine 1.4 mg/m^2 i.v. 1st day; prednisone 40 mg/m^2 p.o. for 14 days; procarbazine 100 mg/m^2 p.o. for 7 days; doxorubicin 35 mg/m^2 i.v. 7th day, bleomycin 10 mg/m^2 i.v. 7th day, vinblastine 6 mg/m^2 i.v. 7th day). This cycle was repeated every 28 days and followed by involved field radiotherapy of 25 Gy. A complete response was attained after 6 courses of chemotherapy which continued after radiotherapy. The pain and swelling of the joints and the tenderness in the lower legs, arms, fingers, and toes diminished by the third course of chemotherapy. The clubbing regressed at the end of therapy. The patient is symptom-free 9 months after completion of therapy.

DISCUSSION

Hypertrophic osteoarthropathy (HOA) was first described by Bamberger in 1889 [12] and Marie in 1890 [13] in association with intrathoracic inflammatory lesions. HOA syndrome can be either primary or secondary [1,14,24]. Primary HOA and secondary HOA are two distinct clinical entities as manifested by clinical and radiological findings and also in treatment. Primary familial HOA is extremely rare, and is not associated with an underlying disease. It has been associated with myeloid metaplasia and skin changes. The prognosis of primary HOA is good and the changes may resolve spontaneously [4,14]. Secondary HOA has been associated with various underlying pulmonary and nonpulmonary causes, including intrathoracic tumors, cystic fibrosis, cyanotic congenital heart disease, liver disease, biliary atresia, inflammatory bowel disease, Graves' disease, and chronic lung diseases [2,3]. Neoplastic disorders are among these intrathoracic tumors and account for 92% of the HOA cases in adults, whereas only 12% of HOA in childhood has been associated with neoplasia [5]. Secondary HOA, is also called hypertrophic pulmonary osteoarthropathy when there is an underlying pulmonary cause. The presentation and symptoms of HOA that are not associated with tumors are similar to those associated with neoplasia, and relief of symptoms with therapy of the underlying disease is similar in both groups.

From 1890–1996 only 28 children, including our case, under the age of 18 years with malignancy and associated HOA have been reported [3,6–11]. All but two were over 10 years of age and 21 [75%] were males.

Fig. 2. An X-ray of the tibia and fibula showing diffuse periosteal reactions and thickened cortices.

Eleven of these patients were diagnosed with nasopharyngeal carcinoma, 8 with osteosarcoma, 5 with Hodgkin lymphoma, 2 with thymus carcinoma, 1 with a periosteal sarcoma, and 1 with a pleural mesothelioma. (Table 1) demonstrates the characteristics of the five cases of childhood Hodgkin disease that were associated with HOA.

Radiologic findings of HOA are usually characteristic. Periosteal new bone formation is seen as a thin opaque line of new bone formation separated from the bony cortex by a narrow translucent band. Later, the two layers of bone gradually fuse and lamellar patterns of periosteal new bone may be seen [1,9]. Although periosteal new bone formation is a hallmark of HOA, it has also been described as a radiologic manifestation of Hodgkin bone disease. In Hodgkin bone disease the periosteal reaction is most often seen on the anterior surface of the lumbar vertebrae, occasionally in the long bones, but rarely without evidence of underlying cortical bone destruction [9,15]. There was no cortical bone destruction in our patient, nor are there any in the previous cases of documented Hodgkin disease and HOA.

HOA may precede the neoplastic pulmonary symptoms by 1–18 months [3]. In our patient HOA appeared prior to symptoms associated with the Hodgkin disease, and in fact led to its discovery. Although information on the reversibility of symptoms associated with HOA in the other cases of childhood Hodgkin disease is unknown, as it was in our patient, complaints associated with HOA may be reversible after successful treatment of the lung abnormality [1,3,11].

The presence of HOA has been thought to be a bad prognostic sign, since most of the patients with malignancy and HOA have either died or showed extensive metastases at the end of follow-up [3]. The mean survival of patients with HOA and cancer was about 9 months; with only 1 subject living more than 2 years [3]. Most of the cases in the literature were reported before 1980, with only five thereafter [3,6,7].

These poor results probably reflect the malignancy of the underlying cancer rather than any impact of the HOA itself. Improved survival achieved by modern treatments may result in better prognosis for these children. Our case has completed treatment successfully, and is disease-free on follow-up, albeit for only 9 months after completing treatment.

Although the pathogenesis of HOA is unknown, estrogens, various circulatory and neurogenic factors, and growth hormones produced by the tumor have been postulated to play a role by stimulating periosteal growth [1,13]. Another theory is that arteriovenous shunts allow the escape of an unknown ''hormone'' or ''toxin'' into the systemic circulation of patients with intrathoracic disease resulting in HOA. It has been suggested that afferent impulses traveling through the vagal or intercostal nerves from the pulmonary lesion to the central nervous system may be responsible for the symptoms of HOA; this has been clinically supported by the patients' relief of symptoms after vagotomy or after transection of the intercostal nerves [1,3].

In conclusion, HOA occurring with a malignant tumor is very rare in children with 28 published cases, 5 of whom were associated with Hodgkin disease, including the present patient. The appearance of HOA in a child with a tumor has been reported to be a bad prognostic sign. The exact etiology of HOA is still unknown. It is important that patients with symptoms of HOA and intrathoracic mass be examined carefully to rule out a malignancy.

TABLE I. Characteristics of Children With HOA and Hodgkin Disease Published in the Literature

Author	Age, sex (years)	Chest X-ray*	Reversal of HOA complaints	Outcome	Therapy		Survival (months)	
					CT	RT	a	b
Canciulescu et al. [7]	6,M	+	x	x	x	x	x	x
Adler and Sharma [8]	12,M	+	−	Died	Nitrogen mustared corticosteroids	+	24,	14
Kay et al. [10]	11,M	+	x	x	−	+	x	x
Shapiro and Zvaifler [9]	16,F	+	x	Died	x	x	12,	1
Present case	12,M	+	+	NED	MOPP/ABV	+	10,	15

*Abnormalities on chest X-ray at onset of HOA.
NED: no evidence of disease.
x: unknown.
a: after onset of HOA.

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REFERENCES

1. Bunn PA, Ridgway EC: Hypertrophic pulmonary osteoarthropathy. In Devita VT, Hellman S, Rosenberg SA (eds): ''Cancer, Principles and Practice of Oncology.'' Philadelphia: J.B. Lippincott Company, 1989, pp. 1931–1932.
2. Cavanough JJA, Halman GH: Hypertrophic osteoarthropathy in childhood. J Pediatr 66:27–40, 1965.
3. Staalman CR, Umans U: Hypertrophic osteoarthropathy in childhood malignancy. Med Pediatr Oncol 21:676–679, 1993.
4. Vogl A, Goldfischer S: Pachydermoperiostitis: Primary or idiopathic hypertrophic osteoarthropathy. Am J Med 33:166–187, 1962.
5. Draouat S, Khellaf M, Aissaou A, Forest M: A propos d'une maladie de Pierre-Marie-Bomberger chez un enfant. Ann Radiol 29:539–543, 1986.
6. İlhan İ, Kutluk T, Göğüş S, Besim A, Büyükpamukçu M: Hypertrophic pulmonary osteoarthropathy in a child with thymic carcinoma: An unusual presentation in childhood. Med Pediatr Oncol 23:140–143, 1994.
7. Canciulescu E, Hirsch R: Recherches faites dans un cas de Hodgkin médiastino-pleural sur la physio pythologie des doigt hippocrates. Bull et mem de la Soc méd des hôp de Bucharest 9:133, 1929.
8. Adler JJ, Sharma OP: Hypertrophic osteoarthropathy with intrathoracic Hodgkin's Disease. Am Rev Resp Dis 102:83–85, 1970.
9. Shapiro RF, Zvaifler NJ: Concurrent intrathoracic Hodgkin's Disease and hypertrophic osteoarthropathy. Chest 63:912–916, 1973.
10. Kay CJ, Rosenberg MA, Burd R: Hypertrophic osteoarthropathy and childhood Hodgkin's Disease. Radiology 112:177–178, 1974.
11. Petty RE, Cassidy JT, Heyn R, Kenien AG, Washburn RL: Secondary hypertrophic osteoarthropathy: An unusual cause of arthritis in childhood. Arthritis Rheum 19:902–906, 1976.
12. Bamberger E: Bronchiektasie und Veranderungen einzelner Röhren knochen. Sitzung der K.K. Gesellch. der Aerzte von 8 Marz 1889. Wiener Klin Wochenschr 2:226, 1889.
13. Marie P: De l' ostéo-arthropathie hypertrophiante pneumique. Rev Med 10:1–36, 1890.
14. Diren B, Kutluk MT, Kanabent A, Göçmen A, Adalioğlu G, Kenanoğlu A: Primary hypertrophic osteoarthropathy. Pediatr Radiol 16:231–234, 1986.
15. Mirra JM: Lymphoma and lymphoma-like disorders. In Mirra JM, Picci P, Gold RH (eds): ''Bone Tumors.'' Clinical, radiologic and pathologic considerations. Philadelphia: Lea & Febiger, 1989, pp. 1121–1185.